The Sniffing Kidney: Roles for Renal Olfactory Receptors in Health and Disease

Blythe D. Shepard (iD)

Abstract

Olfactory receptors (ORs) represent the largest gene family in the human genome. Despite their name, functions exist for these receptors outside of the nose. Among the tissues known to take advantage of OR signaling is the kidney. From mouse to man, the list of renal ORs continues to expand, and they have now been linked to a variety of processes involved in the maintenance of renal homeostasis, including the modulation of blood pressure, response to acidemia, and the development of diabetes. In this review, we highlight the recent progress made on the growing appreciation for renal ORs in physiology and pathophysiology.

Introduction

G protein-coupled receptors (GPCRs) are the largest gene family in the genome and are involved in almost every aspect of physiology, ranging from hormonal regulation to eyesight. These receptors also happen to represent the largest class of "druggable" proteins; in fact, 20–30% of all FDA-approved drugs target GPCRs (1,2). However, only a small subset of this protein family is being actively studied, leaving behind an extensive list of underappreciated GPCRs. Included in this list are the "sensory" GPCRs, which consist of taste receptors, opsins, and olfactory receptors (ORs).

Although ORs are known to govern one's sense of smell, it has become clear these receptors are expressed in extranasal tissues including sperm, muscle, skin, adipose, and the gastrointestinal tract, with functions ranging from cell migration and motility to hormone release (3–7). The kidney in particular is a "sensory organ," the tubular epithelial cells and renal vasculature are tasked with monitoring the composition of the blood and ultrafiltrate to adjust filtration, reabsorption, and secretion accordingly. Given this, it is no wonder that chemosensory ORs have emerged as major factors in the maintenance of renal homeostasis. Although the list of renal ORs is constantly expanding, most of these receptors remain orphan receptors with no known functions and/or localization (8–10) (Figure 1; Table 1). Nonetheless, several renal ORs have emerged as key contributors to kidney physiology. This review focuses on the established and emerging roles of renal ORs in both health and disease and highlights the clinically relevant future directions.

OR Signaling in the Nose and Kidney

ORs are members of the Class A Rhodopsin GPCR family. They are also the largest single class of proteins, making up nearly 0.1% of the human genome (25). Although there are more than 350 human ORs, there are more than 1000 within the mouse and rat, making the identification of functional orthologs a challenge (26,27). Throughout this review, references will be made to human, mouse, and rat ORs, and all three species have slightly different naming conventions (26,28,29). Human ORs are grouped into gene families and subfamilies on the basis of phylogenetic classification. They begin with the prefix "OR" followed by a family-subfamily-individual gene classification (*e.g.*, OR51E2 is a human OR in gene family 51, subfamily E, gene 2). For mouse ORs, two naming systems dominate. They are either grouped by subfamilies using the prefix "MOR" or on the basis of their location within the genome using the prefix "Olfr" (*e.g.*, MOR256–24 = Olfr1393). Finally, for rat ORs, the prefix "Olr" is used followed by a gene number on the basis of chromosome localization (*e.g.*, Olr59).

Despite thousands of gene polymorphisms that modulate an individual's sense of smell, these receptors are extremely similar at the molecular level and all signal through a conserved downstream signaling cascade (30–32). In the nose, ORs are localized to the cilia on the olfactory sensory neurons, which ensures they are exposed to a wide variety of volatile odorants. On odorant binding, the trimeric G protein ($G_{olfactory}$ or G_{olf}) dissociates into active α and $\beta\gamma$ subunits, with the α subunit triggering activation of adenylate cyclase 3 (AC3) (30–32). As the field of OR biology expands, these conserved signaling proteins have been found in other tissues as well. Although it is unclear if extranasal ORs can couple to other G proteins outside of the olfactory epithelium, a role for this signaling cascade exists within the kidney (Figure 2). In fact, studies using the AC3 knockout (KO) mouse were the first to indicate that ORs and OR signaling have important contributions to renal homeostasis (11).

Department of Human Science, Georgetown University, Washington, DC

Correspondence: Blythe D. Shepard, Department of Human Science, Georgetown University, School of Nursing and Health Studies, 263 St. Mary's Hall, 3700 Reservoir Road NW, Washington, DC 20057. Email: blythe.shepard@georegetown.edu
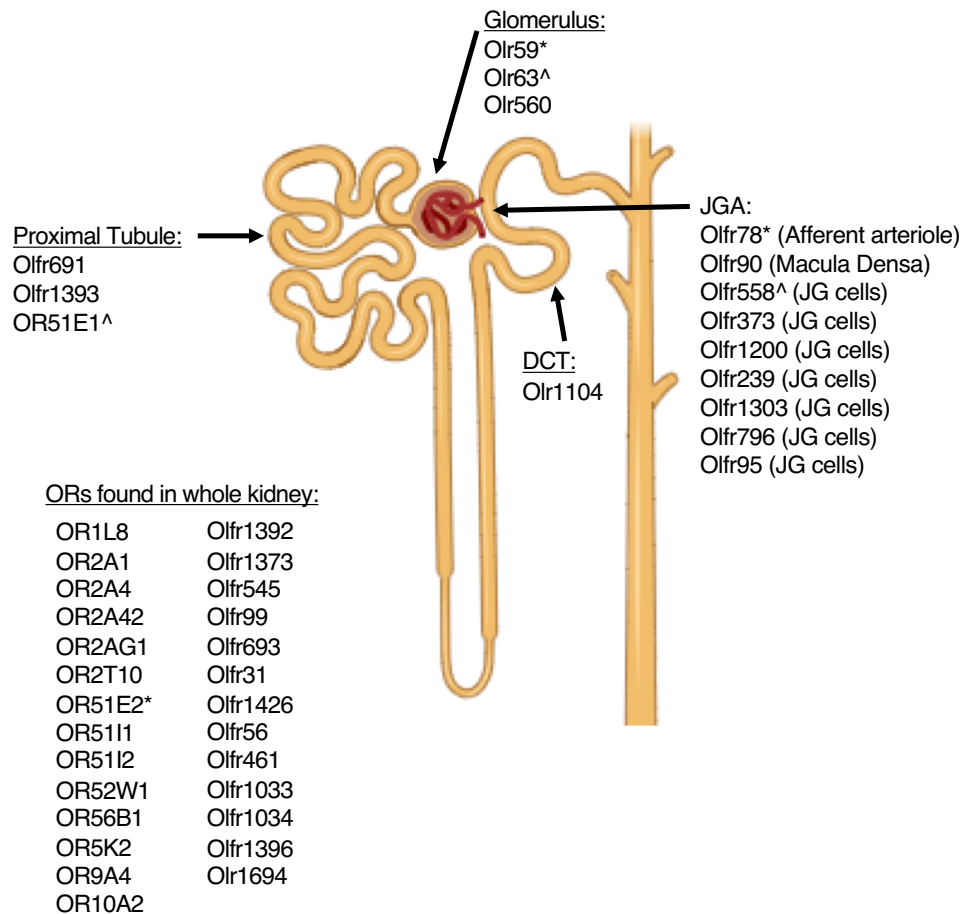
Figure 1. | Renal olfactory receptors. The mouse, rat, and human kidneys are known to express a growing list of olfactory receptors (ORs). Although the localization of most remains unknown (list on the left), several of these have been identified in distinct parts of the nephron. As listed, human ORs begin with the prefix "OR," murine ORs begin with "Olfr," and rat ORs start with "Olr." *Murine Olfr78, rat Olr59, and human OR51E2 are functional orthologs. ^Murine Olfr558, rat Olr63, and human OR51E1 are functional orthologs.

Blood Pressure Control

Both AC3 and G_{olf} have been shown to be expressed in the human and murine kidney at both the transcript and protein level (11). Antibody labeling places murine AC3 specifically within the macula densa (MD) and G_{olf} primarily within the distal convoluted tubule (both at the MD and surrounding epithelial cells) (11). Given the role of the MD in monitoring tubular fluid to control glomerular filtration and renin secretion, it is tempting to speculate that renal ORs are involved in these processes. Indeed, AC3 KO mice have a decreased GFR and lowered plasma renin levels (11). This correlates with a reduction in potassium excretion and an upregulation of COX-2 and nNOS activity that is likely a result of a feedback mechanism. Although the exact OR responsible for these processes is unknown, full-length gene expression of Olfr90 (MOR256–21) was found in an MD cell line (11). An orphan receptor at the time, it has since been deorphanized and determined to respond to a wide range of compounds that are closely aligned with fungal metabolism (the human ortholog is unknown) (14). Although fungi represent a minority of the host microbiome, they do exist in the body as both commensals and toxins, and it is possible the Olfr90-AC3 signaling cascade

could be modulating GFR in response to changing levels of circulating fungal metabolites (Figure 2A). Clearly, future work is needed to examine this possible pathway.

The MD is part of the juxtaglomerular apparatus (JGA), which is a specialized structure formed by both the distal convoluted tubule and the afferent arteriole. It is responsible for synthesizing and secreting renin to regulate blood pressure and GFR, and is home to several renal ORs. Perhaps the most "famous" of these is Olfr78 (MOR18–2; functional orthologs: OR51E2 and Olr59) (11,33–36, 12,13). Olfr78 responds to short chain fatty acids (SCFAs), including acetate and propionate (13). These compounds are bacterial-derived metabolites that are produced by fermentation of dietary fiber by intestinal microbes, and have been linked to a myriad of host functions, including the maintenance of blood pressure (37,38). Using reporter mice and isolated glomeruli, Olfr78 has been localized to the smooth muscle of the major branches of the renal artery and the afferent arteriole (13). Propionate administration promotes renin release from the JGA and leads to an acute drop in blood pressure (13). In Olfr78 KO mice, propionate-induced renin release was all but lost, and the mice were hypersensitive to a drop in blood pressure (13). This is

Table 1.   Confirmed renal olfactory receptors

Human Olfactory Receptors	Mouse Olfactory Receptors	Rat Olfactory Receptors	Known Ligands	References
OR51E2	Olfr78	Olr59	Acetate, propionate, β-ionone, steroid hormones	(11,12,13)
OR51E1	Olfr558	Olr63	Valeric acid, isovaleric acid, methyl valeric acid, cyclobutene-carboxylic acid, norbonene-2-carboxylic acid, methylbutyric acid, hexanoic acid, heptanoic acid, decanoic acid, nonanoic acid, octanoic acid, methyl-nonanoic acid, decanoic acid, propionate, butyrate	(14,15,16,17)
OR2A4			Cyclohexyl salicylate	
OR2AG1			Amylbutyrate	(12)
OR2T10			Maltyl isobutyrate, cinnamaldehyde, vanillin, terpinyl acetate, α-damascone	(18)
OR2A42			α-pinene, farnesol	(19)
OR1L8			Unknown	
OR2A1			Unknown	
OR51I1			Unknown	
OR52W1			Unknown	
OR56B1			Unknown	
OR5K2			Unknown	
OR9A4			Unknown	
OR10A2			Unknown	
OR51I2			Unknown	
	Olfr691		Short and medium chain fatty acids	(20,21)
	Olfr1393		Cycloheptanol, cycloheptanone, cyclooctenone, cyclohexanone, 4,4 dimethylcyclohexanone, nopinone, norcamphor, 4-tertbutylcyclohexanone	(22)
	Olfr90		2-methyl-4-propyl-1,3-oxathiane, 1-octen-3-ol, 3-octanol, 2-octanol, 2-octanone, amyl acetate, linalool, 2-pentylfuran, 3-octanone, benzyl cyanide, 1-octanol, 2-octen-1–0l, allylbenzene, cinnamaldehyde	(14)
	Olfr1200		Citris accord (mixture of limonene, γ-terpinene, citral)	(23)
	Olfr545		Sebacid acid (conflicting reports)	(20,24)
	Olfr1392		Unknown	
	Olfr1373		Unknown	
	Olfr99		Unknown	
	Olfr693		Unknown	
	Olfr31		Unknown	
	Olfr1426		Unknown	
	Olfr56		Unknown	
	Olfr461		Unknown	
	Olfr1033		Unknown	
	Olfr1034		Unknown	
	Olfr1396		Unknown	
	Olfr1694		Unknown	
	Olfr95		Unknown	
	Olfr796		Unknown	
	Olfr1303		Unknown	
	Olfr239		Unknown	
	Olfr373		Unknown	
		Olr560	Unknown	
		Olr1104	Unknown	
		Olr1694	Unknown	

likely due to another SCFA-responsive GPCR, which is found within the renal vasculature that mediates the hypotensive response (GPR41) (39). Collectively, these data indicate that on activation by SCFAs, Olfr78 mediates a hypertensive response. It does so by increasing renin release from the JGA and by changing peripheral vascular resistance (Figure 2A). In addition to Olfr78, the JGA expresses several additional ORs. Microarray analysis of isolated juxtaglomerular cells revealed a total of seven additional murine ORs, whose expression is enriched within this population of cells (34). Among these is Olfr558 (MOR18–1), a carboxylic acid responsive receptor. Along with its rat (Olr63) (36) and human (OR51E1) (15) orthologs, these ORs are activated by butyrate, another SCFA
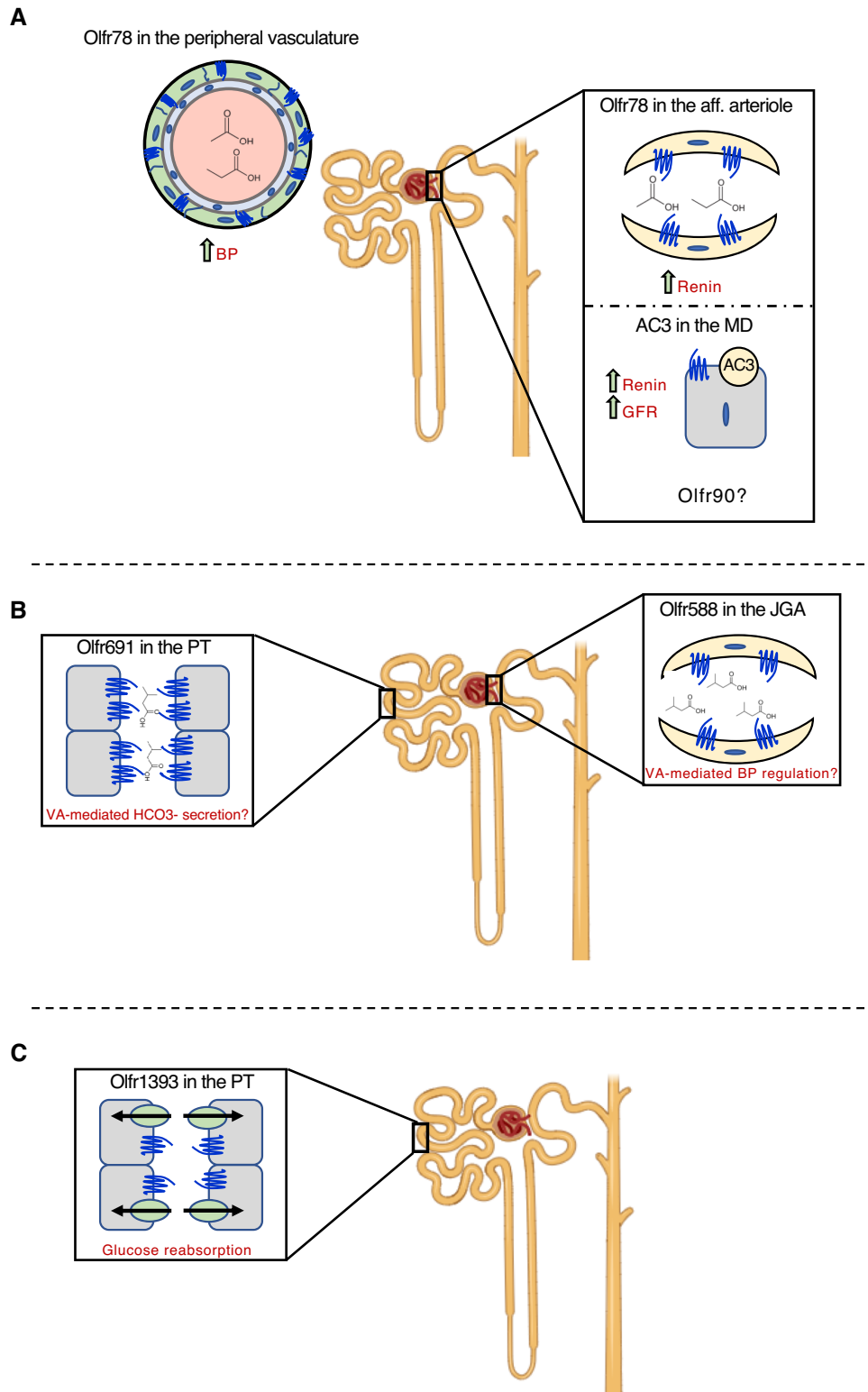
Figure 2. | Proposed functions of select renal olfactory receptors. (A) Olfr78 responds to short chain fatty acids in the peripheral vasculature and the afferent (aff) arteriole to increase BP and promote renin release. Within the macula densa (MD), adenylate cyclase 3 (AC3) has also been linked to an increase in renin release and GFR. Olfr90 has been localized to a MD cell line and may be involved in these processes. (B) Olfr691, localized within the proximal tubule (PT) and Olfr558 (localized to the juxtaglomerular apparatus; JGA) both respond to isovaleric acid (IVA). Under conditions of isovaleric acidemia, these receptors may be involved in bicarbonate secretion and BP regulation. (C) Olfr1393 has been localized within the PT where it contributes to the maintenance of glucose homeostasis via the sodium glucose co-transporters. Its function is exacerbated under conditions of type 1 or type 2 diabetes.

(14–16). Although it remains to be seen if Olfr558 coordinates with Olfr78 to regulate blood pressure, it is certainly notable the JGA expresses ORs that can respond to all three SCFAs, which are known to play protective roles in the kidney via the host microbiome.

ORs and Acidemia

As alluded to above, the host microbiome produces a number of metabolites that contribute to kidney function and many of these activate ORs (40,41). Microbially derived byproducts have been linked to renal protection, including a mitigation of inflammation, decreased reactive oxygen species, and improved renal outcomes after ischemia/reperfusion injury (40–42). In support of this, dysbiosis is associated with a myriad of renal pathogenesis, including inflammation, hypertension, IgA nephropathy, and kidney stone formation (40,41).

Apart from the SCFA butyrate, Olfr588 (found in the JGA) can also respond to several other fatty acids including isovaleric acid (14). This same branched-chain fatty acid activates Olfr588's human ortholog (OR51E1 [15,17,43]; found within human proximal tubule cells) and Olfr691 (MOR31–6), which is localized to the S1 and S3 segments of the renal proximal tubule (20). Isovaleric acid is produced during leucine metabolism and is a known bacterial metabolite (44). Point mutations in the mitochondrial enzyme isovaleryl CoA dehydrogenase prevents the conversion of isovaleryl-CoA to 3-methylcrotonyl CoA, leading to the accumulation of isovaleric acid in the blood and urine, resulting in the metabolic disorder, isovaleric acidemia (45). This acid buildup can lead to life-threatening metabolic acidosis and is cleared via the kidney, where it has potential to activate Olfr588/OR51E1 and Olfr691. It is tempting to speculate that these receptors may sense the excess acid load, and modulate blood pressure (Olfr588) and alter bicarbonate secretion (Olfr691) as a result (Figure 2B). Clearly, these hypotheses require further testing to determine if renal ORs may serve as therapeutic targets for those suffering from organic acidosis and acidemia.

ORs and Diabetes

Recently, several ORs have been linked to adiposity and metabolic balance (7,46–49). The kidney is responsible for filtering all blood glucose and quickly returning it to circulation via reabsorption in the proximal tubule. This task is accomplished in a sodium-dependent manner via two glucose transporters, sodium glucose co-transporter 1 and 2 (SGLT1 and SGLT2, respectively) (50–52). Under euglycemic conditions, this process is seamless; little to no glucose appears in the final urine. However, when glucose concentrations exceed the transport maximum of SGLT1 and SGLT2, glycosuria occurs. Olfr1393 (MOR256–24; human ortholog unknown) is found in all three segments of the renal proximal tubule (via gene expression analysis on hand-dissected nephron segments), where it localizes to the apical membrane when overexpressed in polarized epithelial cells (22). Loss of renal Olfr1393 leads to mild glycosuria and improved glucose tolerance despite euglycemia and normal plasma and urinary electrolytes (22). Coupled

with this phenotype was the observation that SGLT1, the transporter responsible for reabsorbing approximately 10% of glucose under normal conditions, was mislocalized in Olfr1393 KO mice (22) (Figure 2C). Given the emerging roles for these transporters in the treatment of diabetes (SGLT2 inhibitors are extensively reviewed elsewhere) (53–57), we wondered if Olfr1393 KO mice may exhibit an altered diabetic phenotype. Using a high-fat diet to induce obesity and early stages of type 2 diabetes (58), we observed that Olfr1393 KO mice had improved glucose tolerance and an attenuation in diabetes-induced hyperfiltration. Similar findings are observed in Olfr1393 KO mice challenged with streptozotocin to induce pancreatic beta cell depletion and type 1 diabetes. It is worth noting that much of these findings with Olfr1393 KO mice were found to be sex dependent, shedding new light on sex differences with glucose homeostasis (58,59). Moreover, Olfr1393 was found to be activated by small cyclic compounds, and the physiologic relevance of these is still under investigation (Table 1). Identification of physiologic ligands and the functional human ortholog for Olfr1393 will be necessary to appreciate the translational potential for this receptor.

Anosmia and the Kidney?

Although the sense of smell is often taken for granted, those suffering from certain diseases and illnesses (60) know all too well how important functional OR signaling is. The appreciation of this affliction has been heightened by the recent emergence of temporary anosmia as a symptom of SARS-CoV-2 infection (61–63). Does the loss of smell imply a connection between the nose and extranasal ORs? Although it has been postulated that SARS-CoV-2 infection has potential to alter OR signaling throughout the body (64) (including the kidney and bladder), experimental studies in this area are lacking. Despite this, there is a known connection between olfactory and renal function (65,66). In particular, patients suffering from various ciliopathies that are characterized by progressive development of fluid-filled renal cysts, often present with anosmia. Cystic diseases often arise from mutations in select ciliary proteins (*e.g.*, nephrocystin 6, Bardet-Biedl Syndrome proteins), and it has been shown these mutations lead to an altered organization of the olfactory epithelium, including the motile cilia on which ORs reside (66). Future research in this field is clearly needed to appreciate the role that ciliopathies and other anosmia-inducing diseases affect renal OR signaling.

The Future of Renal ORs

To date, 23 murine, five rat, and 15 human ORs have been found to be expressed in the kidney (Figure 1; Table 1). However, the vast majority of these receptors have not been studied in a molecular or physiologic context. This research is hindered by the lack of available reagents for this class of proteins (10) (reliable antibodies are rare, most are orphan receptors, ortholog identification is challenging). Given the physiologic relevance of the few renal ORs that have been characterized thus far (Figure 2), the future is ripe for renal OR research. In fact, expression of these receptors is not confined to the kidney, as there is evidence

that the entire urinary system uses OR signaling as a means for maintaining function. Both human (OR10H1) and murine (Olfr895, Olfr544, Olfr1392, Olfr181) ORs have been found in the bladder, and it is notable that some of these are the same as those found in the kidney (67,68). In particular, evidence has emerged that some of these receptors may be highly expressed in bladder cancers (renal carcinomas have not been examined) and activation of these receptors may represent a novel therapeutic treatment option (69). These recent findings align with previous studies showing that several ORs are known biomarkers for various cancers (renal ORs OR51E1 and OR51E2 are highly expressed in prostate cancer) (69). As this field expands, increased identification and characterization of ORs throughout the urinary system will undoubtedly expand our current appreciation for this signaling pathway in both health and disease.

Author Contributions

B Shepard was responsible for the funding acquisition and investigation, wrote the original draft, and reviewed and edited the manuscript.

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